April 4, 2007

Mr. John Morris
American Chemistry Council
Aliphatic Esters Panel
1300 Wilson Boulevard
Arlington, VA 22209

Dear Mr. Morris:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Polyol Esters Category posted on the ChemRTK HPV Challenge Program Web site on September 21, 2004. I commend the Aliphatic Esters Panel for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact me at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Mark Townsend, Chief
HPV Chemicals Branch

Enclosure

cc: O. Hernandez
C. Augustyniak
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
Polyol Esters Category of the Aliphatic Esters Chemicals

SUMMARY OF EPA COMMENTS

The sponsor, the American Chemistry Council's Aliphatic Esters Panel, submitted a test plan and robust summaries for the revised Polyol Esters Category, dated August 24, 2004 in response to EPA's comments on the previously submitted Aliphatic esters category that were posted on the website on August 28, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on September 21, 2004. The category consists of 16 substances. Robust summaries were also submitted for four structural analogs: trimethylolpropane esters of heptanoic acid and octanoic acid (CAS No. 189120-64-7); hexanedioic acid, mixed esters with C10-rich, C9-11 isoalcohols and trimethylolpropane (CAS No. 180788-27-6); hexanedioic acid mixed esters with heptanoic, octanoic, and decanoic acid and pentaerythritol (CAS No. 68130-55-2); and pentaerythritol esters of isooctanoic acid and C8-10 fatty acids (no CAS No. assigned).

EPA has reviewed this submission and has reached the following conclusions:

1. Category Definition. The category definition is clear.

2. Category Justification. Similarities in chemical structure and in physicochemical, environmental fate, and toxicological properties support the grouping of these chemicals. Their further grouping into subcategories based on the parent polyol ester is also supported; however, two members of the trimethylolpropane subcategory (CAS No. 11138-60-6 and CAS No. 70024-57-6), should be considered separately because they differ in the physicochemical properties that could influence their bioavailability.

3. Analog Justification. Three of the four proposed analog substances are reasonable. The remaining analog, hexanedioic acid mixed esters with heptanoic, octanoic, and decanoic acid and pentaerythritol (CAS No. 68130-55-2), is structurally different from the sponsored substances and the other analogs, because it contains a free carboxylic acid group that may affect its toxicity to mammals and aquatic species. The submitter needs to provide further justification for the use of this analog.

4. Physicochemical Properties. The submitter needs to present all physicochemical data in robust summary format (except for CAS Nos. 11138-60-6 and 126-57-8). The submitter needs to delete the anomalous calculated melting point values from Table 2, and instead provide a technical discussion on the melting points of these chemicals.

5. Environmental Fate. The submitter needs to present all environmental fate data in robust summary format, except for the submitted biodegradation data, and explain how biodegradation data are extrapolated/interpolated among the category members.

6. Health Effects. The submitter needs to expand the use of available dermal absorption data to support the developmental toxicity endpoint; provide robust summaries for the reproductive toxicity endpoint; and address deficiencies in the robust summaries.

7. Ecological Effects. The submitted data are adequate to address all aquatic endpoints for the purposes of the HPV Challenge Program.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE POLYOL ESTERS CATEGORY CHALLENGE SUBMISSION

Category Definition

This submission covers 16 aliphatic esters composed of a polyhydroxy alcohol (polyol) and 1-6 fatty acids and ranging in carbon number from C24 to C77 (with a molecular weight range of 415-1202). These are esters of either a single fatty acid or of a mixture of fatty acids. The submitter divided the sponsored substances into three subcategories based on the parent polyol: trimethylolpropane (TMP), pentaerythritol (PE), or dipentaerythritol (diPE). The carboxylic acid portion of the esters is derived from saturated or unsaturated fatty monoacids ranging in carbon number from C5-C18. The sponsored compounds are listed below, grouped according to parent polyol subcategories as presented in the test plan.

Trimethylolpropane (TMP)	CAS No:
Decanoic acid, mixed esters with heptanoic acid, octanoic acid, and trimethylolpropane	68130-53-0
Decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate	11138-60-6
Nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol	126-57-8
Fatty acids, C14-18 and C16-18 unsaturated, triesters with trimethylolpropane	68002-79-9
9-Octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol	70024-57-6
9-Octadecenoic acid (Z)-, 2-ethyl-2-[[(1-oxo-9-octadecenyl)oxy]methyl]-1,3-propanediyl ester, (Z)-	57675-44-2
Pentaerythritol (PE)	**CAS No:**
Carboxylic acids, C5-9, tetraesters with pentaerythritol	67762-53-2
Decanoic acid, mixed esters with heptanoic acid, isovaleric acid, octanoic acid, and pentaerythritol	68130-51-8
Fatty acids, C5-10, esters with pentaerythritol	68424-31-7
Fatty acids, C5-10, mixed esters with pentaerythritol and valeric acid	68424-34-0
Nonanoic acid, neopentanetetrayl ester	14450-05-6
Pentaerythritol, tetrastearate	115-83-3
Linseed oil, ester with pentaerythritol	68648-28-2
Fatty acids, tall oil, tetraesters with pentaerythritol	68334-18-9
Dipentaerythritol (diPE)	**CAS No:**
Fatty acids, C5-10, esters with dipentaerythritol	70983-72-1

Carboxylic acids, C5-9, hexaesters with dipentaerythritol 67762-52-1

Category Justification

The submitter's rationale for grouping the sponsored substances into a single category is based primarily on their structural and chemical similarities (i.e., polyol esters) that result in "close commonalities" in physicochemical and toxicological properties.

All the sponsored substances and analogs contain a polyhydroxy alcohol and at least one ester function. The sponsored substances, however, differ in the number of ester functions (1-6), the length of the carboxylic acid function (C5-C18), and the extent of unsaturation of the carboxylic acid group. These structural differences are expected to result in a range of physicochemical properties, especially partition coefficient and water solubility, and a range of associated environmental fate and toxicological properties.

All but two of the sponsored substances have low water solubility and vapor pressure, high lipophilicity, and similar environmental fate properties (biodegradation, photodegradation, hydrolysis and fugacity). Mammalian toxicity data for acute, repeated-dose and genetic toxicity support grouping of these substances. The high molecular weights (>500) of the fully esterified substances should limit their uptake from the gastrointestinal tract, and thus similar toxicity is expected among these 14 category members. Available ecotoxicity data also lend support for grouping of these chemicals.

The two substances, decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate (a TMP diester, CAS No. 11138-60-6) and 9-octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (a TMP monoester, CAS No. 70024-57-6), contain unesterified alcohol groups and are thus structurally different from the other members. These TMP mono- and diesters are the only sponsored chemicals that have molecular weights below 500, log K_{ow} values below 10, and water solubilities above 10^{-6} mg/L, and that may be metabolized differently than the other sponsored substances because of the available hydroxyl group. Therefore, these two substances need to be considered as a separate subgroup for both health and ecological effects.

Analog Justification

The structures of three of the four analogs are similar to the sponsored substances and are expected to be representative of the esters in their respective subcategories (i.e., TMP and PE esters). The remaining analog, hexanedioic acid mixed esters with decanoic acid, heptanoic acid, and octanoic acid and pentaerythritol (CAS No. 68130-55-2), is structurally different from the sponsored substances because it has a free carboxylic acid group. Because the carboxyl group may affect its toxicity to mammals and aquatic species in comparison with the sponsored substances, this substance is not considered an appropriate analog from structural similarities alone. The submitter needs to provide further justification (e.g., metabolic profiling data) for this analog.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The submitter used incorrect structures when estimating the data for CAS Nos. 70024-57-6 and 67762-53-2.

Although mostly calculated values are provided for these endpoints, the submitter needs to present all l data in robust summary format. It is not sufficient to present the data only in Table 2 of the test plan.

Most of the data provided by the submitter for boiling point, vapor pressure, octanol/water partition coefficient, and water solubility are adequate for the purposes of the HP Challenge Program.

Melting point. The measured pour point value of -61 ^{o}C for CAS No. 126-57-8 is adequate for the purposes of the HPV Challenge Program. However, there is a large difference between this value and the calculated value for this chemical of 193 °C. Similarly, the submitter provided a measured melting point of < -25 ^{o}C but a calculated value of 157 ^{o}C for the analog CAS No. 189120-64-7, and EPA located a melting point for pentaerythritol tetrastearate (CAS No. 115-83-3) of 66-77 ^{o}C (Beilstein), versus the sponsor's calculated value of 350 ^{o}C (the published value should be added to the submission). The chemical structures of these substances also indicate that it is unlikely that they will have such high melting points. Thus, the calculated melting points in Table 2 of the test plan cannot be considered realistic. The footnotes to Table 2 do not fully address this issue. The submitter needs to provide a technical discussion of melting points for these substances in the test plan, include it in the robust summaries, and delete the calculated values from Table 2. The submitter needs to provide a measured melting point for nonanoic acid neopentanetetrayl ester and any other substances that are not mixtures.

Boiling point. EPA identified an experimental boiling point of 204-211 ^{o}C (0.1 Torr) for nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propandiol was located (Beilstein 2005). This value was normalized to 462.8-472.8 ^{o}C by NOMO5 using a classification of 3.

Environmental Fate (photodegradation, stability in water, biodegradation and fugacity)

The submitter needs to present all environmental fate data in robust summary format. It is not sufficient to present the data in Table 2 of the test plan alone.

Photodegradation. The submitter needs to provide estimated photodegradation data for CAS Nos. 68424-31-7, 68424-34-0, 70983-72-1, and 67762-52-1. The submitter needs to verify the structures for CAS Nos. 70024-57-6 and 67762-53-2 prior to estimating their photodegradation values.

Stability in water. The submitter needs to use corrected mixed-ester structures for CAS Nos. 11138-60-6 and 68130-51-8 to estimate their stability in water values.

Biodegradation. The biodegradation data provided by the submitter are adequate for the purposes of the HPV Challenge Program. However, the submitter needs to indicate how biodegradation values will be used for read-across purposes (interpolated or extrapolated).

Transport and distribution. The data provided by the submitter are adequate for the purposes of the HPV Challenge Program. However, the submitter needs to present the data in robust summary format and include the input values used in the fugacity estimation for each chemical.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

There are data gaps for the diPE subcategory for these endpoints. However, the members have molecular weights above 500, suggesting limited absorption from the gastrointestinal tract. This is supported by the acute toxicity data and data from the TMP and PE subcategories. Therefore, no further testing is indicated for the purposes of the HPV Challenge Program.

For the TMP and PE ester subcategories, adequate data were submitted for the acute, repeated-dose and genetic toxicity endpoints for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

Reproductive/developmental toxicity. Owing to the irritant nature of the sponsored substances, and because they are used in lubricant formulations, the use of dermal exposure data is appropriate for this case. No data are available for the reproductive toxicity endpoint. The submitter needs to summarize data from the 13-week repeated-dose dermal toxicity studies (evaluation of reproductive organs—organ weights, gross and histopathology) and the developmental toxicity studies, in robust summary format, to address the reproductive toxicity endpoint. For developmental toxicity, dermal studies are considered incomplete without supporting data on the dermal absorption of the test substance. However, in the

repeated-dose dermal toxicity study robust summary for CAS No. 67762-53-2, the submitter states that the dermal bioavailability of the test article was 2 to 6%. This information needs to be expanded and included in the robust summaries where developmental toxicity was tested via the dermal route of exposure. Also, the submitter needs to evaluate maternal toxicity on the basis of signs of systemic toxicity rather than local effects such as skin irritation.

Ecological Effects (fish, invertebrates, and algae)

The submitted data are adequate to address all aquatic endpoints for both fully esterified sponsored chemicals and the TMP mono- and diesters.

Specific Comments on the Robust Summaries

Health Effects

General. Test substance purity is missing in some robust summaries and should be stated, if available.

Genetic Toxicity (chromosomal aberrations). The summary of the *in vitro* test with CAS No. 189120-64-7 did not report the number of metaphases scored per concentration.

Developmental Toxicity. The summary of the study on CAS No. 11138-60-6 lacks information on whether the test material was applied to clipped intact skin or abraded skin. The summary of the study on CAS No. 67762-53-2 is missing details on the specific developmental toxicity parameters that were examined.

Ecological Effects

Fish. None of the three summaries reported mean fish weight or age. The summary of the study on CAS No. 11138-60-6 did not provide detailed results of the analytical monitoring. The summary of the study on CAS No. 70024-57-6 did not report loading, and did not specify test substance purity. The summary of the study on CAS No. 189120-64-7 did not report the mean fish weight or fish age.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.